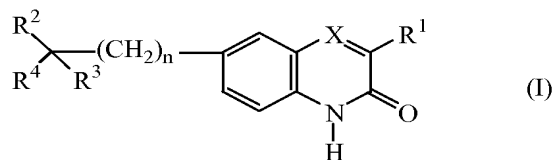


# CLAIMS

1. A compound of formula (I),



the *N*-oxide forms, the pharmaceutically acceptable addition salts and the stereo-chemically isomeric forms thereof, wherein

10 n is 0, 1 or 2;

X is N or CR<sup>5</sup>, wherein R<sup>5</sup> is hydrogen or taken together with R<sup>1</sup> may form a bivalent radical of formula -CH=CH-CH=CH-;

15 R<sup>1</sup> is C<sub>1-6</sub>alkyl or thienyl;

R<sup>2</sup> is hydrogen or hydroxy or taken together with R<sup>3</sup> or R<sup>4</sup> may form =O;

R<sup>3</sup> is a radical selected from

- 20           -(CH<sub>2</sub>)<sub>s</sub>- NR<sup>6</sup>R<sup>7</sup>           (a-1),  
              -O-H                       (a-2),  
              -O-R<sup>8</sup>                     (a-3),  
              -S- R<sup>9</sup>                     (a-4), or  
              —C≡N                   (a-5),

25 wherein

s is 0, 1, 2 or 3;

R<sup>6</sup> is -CHO, C<sub>1-6</sub>alkyl, hydroxyC<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkylcarbonyl, di(C<sub>1-6</sub>alkyl)aminoC<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyloxyC<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkylcarbonylaminoC<sub>1-6</sub>alkyl, piperidinylC<sub>1-6</sub>alkylaminocarbonyl, piperidinyl, piperidinylC<sub>1-6</sub>alkyl, piperidinylC<sub>1-6</sub>alkylaminocarbonyl, C<sub>1-6</sub>alkyloxy, thienylC<sub>1-6</sub>alkyl, pyrrolylC<sub>1-6</sub>alkyl, arylC<sub>1-6</sub>alkylpiperidinyl, arylcarbonylC<sub>1-6</sub>alkyl, arylcarbonylpiperidinylC<sub>1-6</sub>alkyl, haloindozolylpiperidinylC<sub>1-6</sub>alkyl, or arylC<sub>1-6</sub>alkyl(C<sub>1-6</sub>alkyl)aminoC<sub>1-6</sub>alkyl;

R<sup>7</sup> is hydrogen or C<sub>1-6</sub>alkyl;

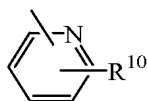
35 R<sup>8</sup> is C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkylcarbonyl or di(C<sub>1-6</sub>alkyl)aminoC<sub>1-6</sub>alkyl; and

$R^9$  is di( $C_{1-6}$ alkyl)amino $C_{1-6}$ alkyl;  
or  $R^3$  is a group of formula

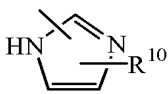


wherein

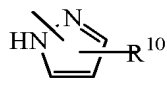
5 Z is a heterocyclic ring system selected from



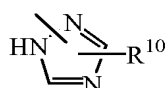
(c-1)



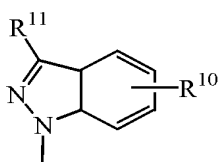
(c-2)



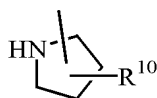
(c-3)



(c-4)



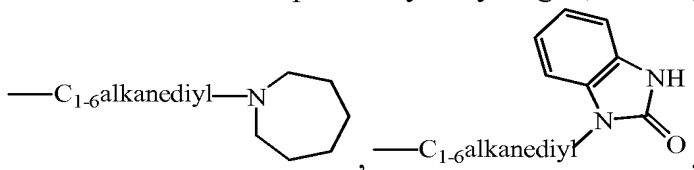
(c-5)



(c-6)

10

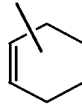
wherein each  $R^{10}$  independently is hydrogen,  $C_{1-6}$ alkyl, aminocarbonyl, hydroxy,



$C_{1-6}$ alkyloxy $C_{1-6}$ alkyl,  $C_{1-6}$ alkyloxy $C_{1-6}$ alkylamino, aryl $C_{1-6}$ alkyl,

di(phenyl $C_{2-6}$ alkenyl), piperidinyl $C_{1-6}$ alkyl,  $C_{3-10}$ cycloalkyl,  $C_{3-10}$ cycloalkyl $C_{1-6}$ alkyl,

15 aryloxy(hydroxy) $C_{1-6}$ alkyl, haloindazolyl, aryl $C_{1-6}$ alkyl, aryl $C_{2-6}$ alkenyl, morpholino,  
 $C_{1-6}$ alkylimidazolyl, or pyridinyl $C_{1-6}$ alkylamino;

$R^4$  is hydrogen,  $C_{1-6}$ alkyl, furanyl, pyridinyl, aryl $C_{1-6}$ alkyl or  ;

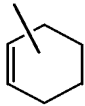
aryl is phenyl or phenyl substituted with halo,  $C_{1-6}$ alkyl or  $C_{1-6}$ alkyloxy;

20

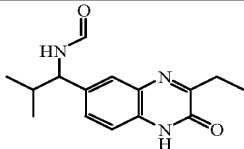
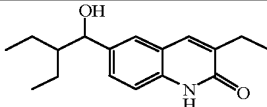
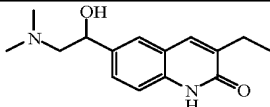
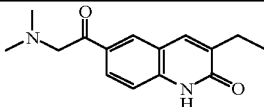
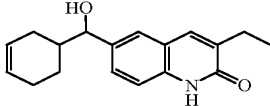
with the proviso that when

n is 0, X is N,  $R^2$  is hydrogen,  $R^3$  is a group of formula (b-1), Z is the heterocyclic  
ring system (c-2) or (c-4) wherein said heterocyclic ring system Z is attached to the  
rest of the molecule with a nitrogen atom, and  $R^{10}$  is hydrogen; then

25  $R^4$  is other than  $C_{1-6}$ alkyl or pyridinyl.

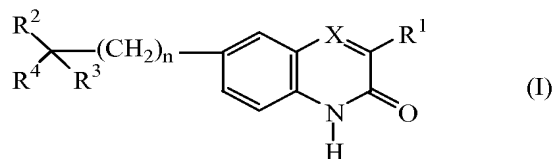
2. A compound as claimed in claim 1 wherein  
 n is 0 or 1; X is N or CR<sup>5</sup>, wherein R<sup>5</sup> is hydrogen; R<sup>3</sup> is a radical selected from (a-1),  
 (a-2) or (a-3) or is a group of formula (b-1) i.e. -Z-; s is 0, 1 or 2; R<sup>6</sup> is -CHO, C<sub>1-6</sub>  
 alkyl, piperidinylC<sub>1-6</sub>alkyl, arylcarbonylpiperidinylC<sub>1-6</sub>alkyl or  
 5 arylC<sub>1-6</sub>alkyl(C<sub>1-6</sub>alkyl)aminoC<sub>1-6</sub>alkyl; R<sup>8</sup> is C<sub>1-6</sub>alkyl; when R<sup>3</sup> is a group of formula  
 (b-1) then Z is a heterocyclic ring system selected from (c-2) or (c-4); and each R<sup>10</sup>  
 independently is hydrogen, C<sub>1-6</sub>alkyl or C<sub>1-6</sub>alkyloxyC<sub>1-6</sub>alkylamino.
3. A compound according to claim 1 and 2 wherein  
 10 n is 0; X is N or CR<sup>5</sup>, wherein R<sup>5</sup> is hydrogen; R<sup>1</sup> is C<sub>1-6</sub>alkyl;  
 R<sup>2</sup> is hydrogen or hydroxy or taken together with R<sup>4</sup> may form =O; R<sup>3</sup> is a radical  
 selected from (a-1) or (a-2); s is 0 or 1; R<sup>6</sup> is -CHO or C<sub>1-6</sub>alkyl; and R<sup>4</sup> is  
 hydrogen, C<sub>1-6</sub>alkyl or .

- 15 4. A compound according to claim 1, 2 and 3 wherein the compound is selected from  
 compound No 1, compound No 5, compound No 7, compound No 3 and compound  
 No 17.

 <p>compound 1</p>	 <p>compound 5</p>
 <p>compound 7</p>	 <p>compound 3</p>
 <p>compound 17</p>	

5. A compound as claimed in any of claims 1 to 4 for use as a medicine.
- 20 6. A pharmaceutical composition comprising pharmaceutically acceptable carriers and  
 as an active ingredient a therapeutically effective amount of a compound as claimed  
 in claim 1 to 4.
- 25 7. A process of preparing a pharmaceutical composition as claimed in claim 6 wherein  
 the pharmaceutically acceptable carriers and a compound as claimed in claim 1 to 4  
 are intimately mixed.

8. Use of a compound for the manufacture of a medicament for the treatment of a PARP mediated disorder, wherein said compound is a compound of formula (I)



5

the *N*-oxide forms, the pharmaceutically acceptable addition salts and the stereochemically isomeric forms thereof, wherein

- 10  $n$  is 0, 1 or 2;

$X$  is N or  $CR^5$ , wherein  $R^5$  is hydrogen or taken together with  $R^1$  may form a bivalent radical of formula  $-CH=CH-CH=CH-$ ;

- 15  $R^1$  is  $C_{1-6}$ alkyl or thienyl;

$R^2$  is hydrogen or hydroxy or taken together with  $R^3$  or  $R^4$  may form  $=O$ ;

$R^3$  is a radical selected from

- 20  $-(CH_2)_s-NR^6R^7$  (a-1),  
 $-O-H$  (a-2),  
 $-O-R^8$  (a-3),  
 $-S-R^9$  (a-4), or  
 $-C\equiv N$  (a-5),

- 25 wherein

$s$  is 0, 1, 2 or 3;

$R^6$  is  $-CHO$ ,  $C_{1-6}$ alkyl, hydroxy $C_{1-6}$ alkyl,  $C_{1-6}$ alkylcarbonyl, di( $C_{1-6}$ alkyl)amino $C_{1-6}$ alkyl,  $C_{1-6}$ alkyloxy $C_{1-6}$ alkyl,  $C_{1-6}$ alkylcarbonylamino $C_{1-6}$ alkyl, piperidinyl $C_{1-6}$ alkylaminocarbonyl, piperidinyl, piperidinyl $C_{1-6}$ alkyl, piperidinyl $C_{1-6}$ alkylaminocarbonyl,  $C_{1-6}$ alkyloxy, thienyl $C_{1-6}$ alkyl, pyrrolyl $C_{1-6}$ alkyl, aryl $C_{1-6}$ alkylpiperidinyl, arylcarbonyl $C_{1-6}$ alkyl, arylcarbonylpiperidinyl $C_{1-6}$ alkyl, haloindozolylpiperidinyl $C_{1-6}$ alkyl, or aryl $C_{1-6}$ alkyl( $C_{1-6}$ alkyl)amino $C_{1-6}$ alkyl;

$R^7$  is hydrogen or  $C_{1-6}$ alkyl;

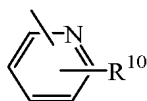
- 35  $R^8$  is  $C_{1-6}$ alkyl,  $C_{1-6}$ alkylcarbonyl or di( $C_{1-6}$ alkyl)amino $C_{1-6}$ alkyl; and

$R^9$  is di( $C_{1-6}$ alkyl)amino $C_{1-6}$ alkyl;  
or  $R^3$  is a group of formula

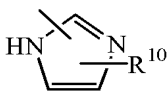


wherein

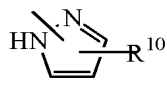
5 Z is a heterocyclic ring system selected from



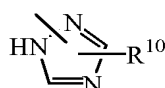
(c-1)



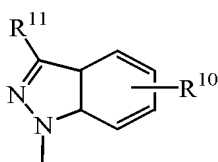
(c-2)



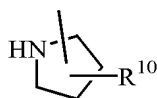
(c-3)



(c-4)



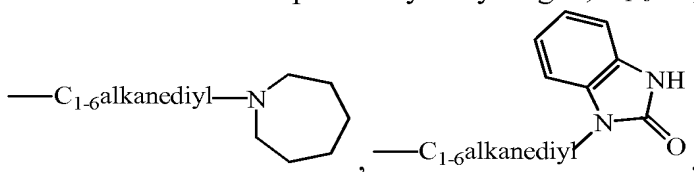
(c-5)



(c-6)

10

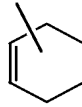
wherein each  $R^{10}$  independently is hydrogen,  $C_{1-6}$ alkyl, aminocarbonyl, hydroxy,



$C_{1-6}$ alkyloxy $C_{1-6}$ alkyl,  $C_{1-6}$ alkyloxy $C_{1-6}$ alkylamino, aryl $C_{1-6}$ alkyl,

di(phenyl $C_{2-6}$ alkenyl), piperidinyl $C_{1-6}$ alkyl,  $C_{3-10}$ cycloalkyl,  $C_{3-10}$ cycloalkyl $C_{1-6}$ alkyl,

15 aryloxy(hydroxy) $C_{1-6}$ alkyl, haloindazolyl, aryl $C_{1-6}$ alkyl, aryl $C_{2-6}$ alkenyl, morpholino,  
 $C_{1-6}$ alkylimidazolyl, or pyridinyl $C_{1-6}$ alkylamino;

$R^4$  is hydrogen,  $C_{1-6}$ alkyl, furanyl, pyridinyl, aryl $C_{1-6}$ alkyl or  ;

aryl is phenyl or phenyl substituted with halo,  $C_{1-6}$ alkyl or  $C_{1-6}$ alkyloxy.

20

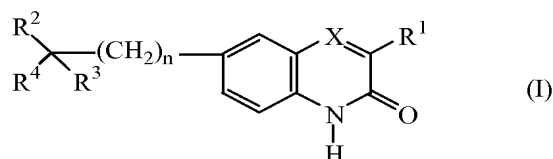
9. Use according to claim 8 of a PARP inhibitor of formula (I) for the manufacture of  
a medicament for the treatment of a PARP-1 mediated disorder

10. Use according to claim 8 and 9 wherein the treatment involves chemosensitization.

25

11. Use according to claim 8 and 9 wherein the treatment involves radiosensitization.

12. A combination of a compound with a chemotherapeutic agent wherein said compound is a compound of formula (I)



5

the *N*-oxide forms, the pharmaceutically acceptable addition salts and the stereochemically isomeric forms thereof, wherein

*n* is 0, 1 or 2;

10

*X* is N or CR<sup>5</sup>, wherein R<sup>5</sup> is hydrogen or taken together with R<sup>1</sup> may form a bivalent radical of formula -CH=CH-CH=CH-;

R<sup>1</sup> is C<sub>1-6</sub>alkyl or thienyl;

15

R<sup>2</sup> is hydrogen or hydroxy or taken together with R<sup>3</sup> or R<sup>4</sup> may form =O;

R<sup>3</sup> is a radical selected from

20

- (CH<sub>2</sub>)<sub>s</sub>- NR<sup>6</sup>R<sup>7</sup> (a-1),
- O-H (a-2),
- O-R<sup>8</sup> (a-3),
- S- R<sup>9</sup> (a-4), or
- C≡N (a-5),

wherein

25

*s* is 0, 1, 2 or 3;

R<sup>6</sup> is -CHO, C<sub>1-6</sub>alkyl, hydroxyC<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkylcarbonyl, di(C<sub>1-6</sub>alkyl)aminoC<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyloxyC<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkylcarbonylaminoC<sub>1-6</sub>alkyl, piperidinylC<sub>1-6</sub>alkylaminocarbonyl, piperidinyl, piperidinylC<sub>1-6</sub>alkyl, piperidinylC<sub>1-6</sub>alkylaminocarbonyl, C<sub>1-6</sub>alkyloxy, thienylC<sub>1-6</sub>alkyl, pyrrolylC<sub>1-6</sub>alkyl, arylC<sub>1-6</sub>alkylpiperidinyl, arylcarbonylC<sub>1-6</sub>alkyl, arylcarbonylpiperidinylC<sub>1-6</sub>alkyl, haloindozolylpiperidinylC<sub>1-6</sub>alkyl, or arylC<sub>1-6</sub>alkyl(C<sub>1-6</sub>alkyl)aminoC<sub>1-6</sub>alkyl;

30

R<sup>7</sup> is hydrogen or C<sub>1-6</sub>alkyl;

R<sup>8</sup> is C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkylcarbonyl or di(C<sub>1-6</sub>alkyl)aminoC<sub>1-6</sub>alkyl; and

35

R<sup>9</sup> is di(C<sub>1-6</sub>alkyl)aminoC<sub>1-6</sub>alkyl;

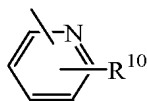
or R<sup>3</sup> is a group of formula



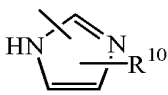
wherein

Z is a heterocyclic ring system selected from

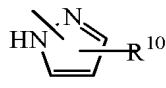
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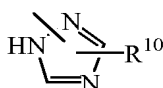
(c-1)



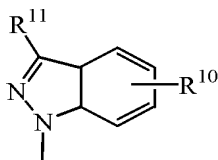
(c-2)



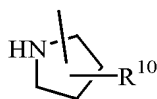
(c-3)



(c-4)

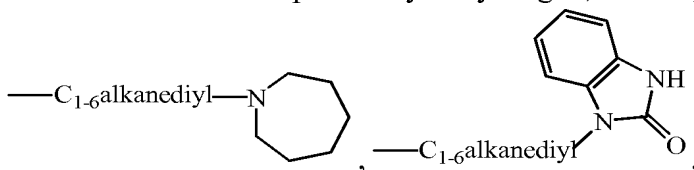


(c-5)



(c-6)

10 wherein each R<sup>10</sup> independently is hydrogen, C<sub>1-6</sub>alkyl, aminocarbonyl, hydroxy,

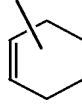


C<sub>1-6</sub>alkyloxyC<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyloxyC<sub>1-6</sub>alkylamino, arylC<sub>1-6</sub>alkyl,

di(phenylC<sub>2-6</sub>alkenyl), piperidinylC<sub>1-6</sub>alkyl, C<sub>3-10</sub>cycloalkyl, C<sub>3-10</sub>cycloalkylC<sub>1-6</sub>alkyl,

aryloxy(hydroxy)C<sub>1-6</sub>alkyl, haloindazolyl, arylC<sub>1-6</sub>alkyl, arylC<sub>2-6</sub>alkenyl, morpholino,

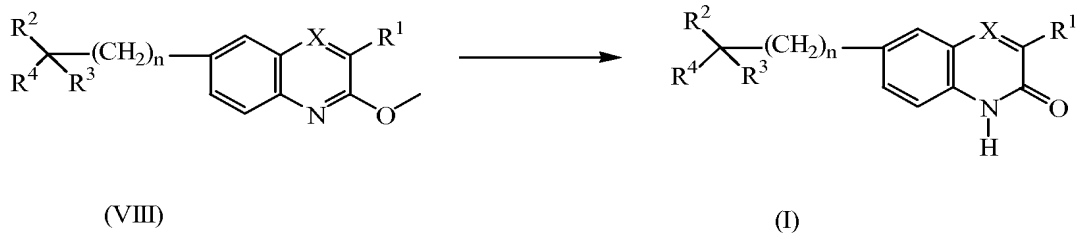
15 C<sub>1-6</sub>alkylimidazolyl, or pyridinylC<sub>1-6</sub>alkylamino;

R<sup>4</sup> is hydrogen, C<sub>1-6</sub>alkyl, furanyl, pyridinyl, arylC<sub>1-6</sub>alkyl or  ;

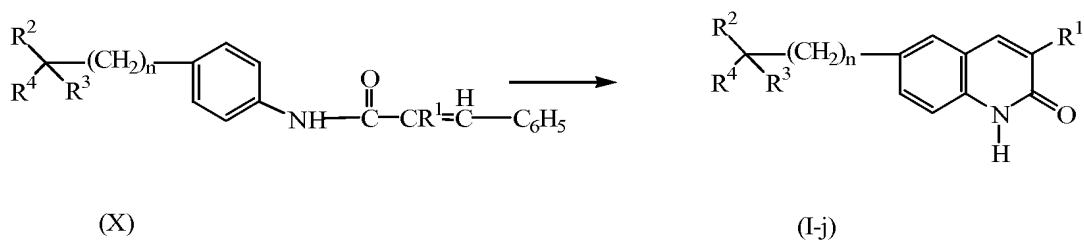
aryl is phenyl or phenyl substituted with halo, C<sub>1-6</sub>alkyl or C<sub>1-6</sub>alkyloxy.

20 13. A process for preparing a compound as claimed in claim 1, characterized by  
a) the hydrolysis of intermediates of formula (VIII), according to art-known methods,  
by submitting the intermediates of formula (VIII) to appropriate reagents, such as,  
tinchloride, acetic acid and hydrochloric acid, in the presence of a reaction inert  
solvent, e.g. tetrahydrofuran.

25



b) the cyclization of intermediates of formula (X), according to art-known cyclizing procedures into compounds of formula (I) wherein X is CH herein referred to as compounds of formula (I-j), preferably in the presence of a suitable Lewis Acid, e.g. aluminum chloride either neat or in a suitable solvent such as, for example, an aromatic hydrocarbon, e.g. benzene, chlorobenzene, methylbenzene and the like; halogenated hydrocarbons, e.g. trichloromethane, tetrachloromethane and the like; an ether, e.g. tetrahydrofuran, 1,4-dioxane and the like or mixtures of such solvents.



c) the condensation of an appropriate ortho-benzenediamine of formula (XI) with an ester of formula (XII) wherein R<sup>h</sup> is C<sub>1-6</sub>alkyl, into compounds of formula (I), wherein X is N, herein referred to as compounds of formula (I-i), in the presence of a carboxylic acid, e.g. acetic acid and the like, a mineral acid such as, for example hydrochloric acid, sulfuric acid, or a sulfonic acid such as, for example, methanesulfonic acid, benzenesulfonic acid, 4-methylbenzenesulfonic acid and the like.

